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ARTHUR R. EGLINGTON
113 Cross Creek Dr. R.D. # 5.
Pottsville, PA 17901

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In response to the status inquiry filed July 6, 2004, a copy of the translation has been forwarded to the BOPAI. Examiner notes that BOPAI will be reviewing the translation once the translation is of record.

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Japanese Patent
Document No. 07-061927

LIPASE INHIBITOR AND FOODS AND BEVERAGES IN WHICH IT IS ADDED
[リパーゼ阻害剤およびこれを添加した飲食品]

Takuo Okuda & Yoshio Ito

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(71) [Applicant]

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390002990

[Name]

KK LOTTE CO., LTD.

[Address]

3-20-1 Nishi-Shinjuku, Shinjuku-ku, Tokyo

(72) [Inventor]

[Name]

Takuo Okuda

[Address]

Within Okayama University, Pharmaceutical Sciences, Tsushima-naka 1-1-1, Okayama City, Okayama Prefecture

(72) [Inventor]

[Name]

Takashi Yoshida

[Address]

Within Okayama University, Pharmaceutical Sciences, Tsushima-naka 1-1-1, Okayama City, Okayama Prefecture

(72) [Inventor]

[Name]

Chikara Hatano

[Address]

Within Okayama University, Pharmaceutical Sciences, Tsushima-naka 1-1-1, Okayama City, Okayama Prefecture

(72) [Inventor]

[Name]

Shimura Shin

[Address]

1-23-6 Numaei, Urawa City, Saitama Prefecture

(72) [Inventor]

[Name]

Yoshio Ito

[Address]

3-26-11 Noen, Kiyose City, Tokyo

(74) [Attorney(s) Representing All Applicants]

[Patent Attorney]

[Name]

Haruo Hamada

(57) [Abstract]

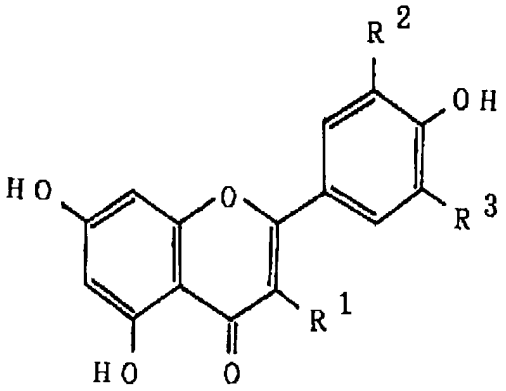
[Objective]

Provides a very safe lipase-inhibiting agent that controls the digestion and absorption of lipids in-vivo and it displays a very high inhibition against pancreatic lipase, which is a key factor in obesity; it obstructs pancreatic lipase and helps control and prevent obesity. In addition, it can be utilized in the prevention of deterioration of foodstuffs and the occurrence of unpleasant odors caused by lipase; and provides foods and beverages in which it [i.e., the lipase-inhibiting agent] has been added and mixed.

[Constitution]

Contains a flavonoid that is shown in formula (1)

[Chemical Formula 1]



[I]

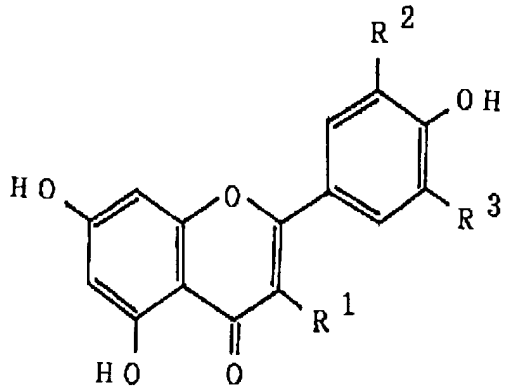
(in the formula, R^1、 R^2 and R^3, are each independent and they show hydrogen atoms or hydroxyl groups) as the effective component of the lipase inhibitor.

[Claim(s)]

[Claim 1]

A lipase inhibitor that is distinguished by the fact that it contains a flavonoid

[Chemical Formula 1]



[I]

that is shown in formula (1) (in the formula, R^1、 R^2 and R^3, are each independent and they show hydrogen atoms or hydroxyl groups) as the effective component of the lipase inhibitor.

[Claim 2]

Foods and beverages that are distinguished by the fact that the lipase inhibitor that is stated in Claim 1 is added or mixed into them.

[Description of the Invention]

[0001]

[Field of Industrial Application]

The invention pertains to a lipase inhibitor. More specifically, it pertains to a lipase inhibitor that effectively obstructs the pancreatic lipase that participates in digestion and absorption of fats in-vivo and can very safely contribute to the control and prevention of obesity.

In addition, this lipase inhibitor can be used to prevent the deterioration of foods and beverages or the occurrence of unpleasant odors caused by lipase.

[0002]

[Prior Art]

In humans, lipase (pancreatic lipase) is the initial enzyme in the digestion and absorption of lipids. Development of drugs to block pancreatic lipase to control/prevent obesity has already been tried.

Examples are the anti-obesity and triglyceride reducing agent that is stated in Japan Unexamined Patent Publication Sho 55-98114, the oxetanone that is stated in、 Japan Unexamined Patent Publication Sho 61- 152663, or the obesity prevention agent that is stated in Japan Unexamined Patent Publication Hei 1- 102022.

[0003]

In addition, with similar objectives, there are also patent publications on foods and beverages to which have been added inhibitors separated from cereals or beans (Japan Unexamined Patent Publication Sho 64- 34264) and extraction methods (Japan Unexamined Patent Publication Sho 49-41580) for inhibitors from seeds that are rich in lipids.

[0004]

Moreover, tannins from fodder leaves (Fodder plants) are known to obstruct lipase (British J. Nutrition, 60, 275 (1988)).

In addition, proteins from soybeans and cereals or radishes are reported to obstruct that (Agricultural and Biological Chemistry (0002 - 1369, ABCHA6), 37 and 1225, (1973), Nurt. Rep. Int.,32, 110 7 (1985), and the journal of Nippon Shokuhin Kogyo K.K. (DB 69-398-6317)、 35, 430 (1988)).

In addition, there are reports on lipase-inhibiting effects from hemicellulose and wheat

bran (Journal of Food Science (ISSN 0022-1147, CODEN JFDAZ), 49,956 (1984), Am. J.Clin. Nutr.,42,629 (1985)), phosphatidyl choline from radish seeds (Meiji University, Faculty of Agriculture research report、73、9 (1986)), and myoinositol (Journal of Food Science (ISSN 0022-1147, CODEN JFDAZ), 53,250 (1988)).

[0005]

In regard to natural medicine, there is a patent publication on fourteen types of natural medicines, including Paeonia lactiflora Pall. And Paeonia suffruticosa Andr. (Tree peony) to act on microorganism lipase, (Japan Unexamined Patent Publication Showa 64-90131).

In addition, results of study on lipase inhibition in regard to various natural extracts has been reported, (Meiji University, Faculty of Agriculture research report、69, 15 (1985)).

[0006]

Moreover, recently, there are patent publications on lipase-inhibiting agents from aqueous extracts such as Capsicum annuum L. (pimenta), pumpkin, mushrooms, edible brown algae, green tea、black tea、and oolong tea (Japan Unexamined Patent Publication Hei 3- 219872) and foodstuffs that control the absorption of lipids that are distinguished by the addition of epigallocatechin gallate which is a principal component in green tea (Japan Unexamined Patent Publication Hei 3- 228664).

[0007]

In contrast, in connection with flavonoids the effects of flavones on small intestine α-glucosidase in rats has been studied with the objective to prevent obesity and diabetes. It is reported that there is an inhibiting effect with myricetin and synthetic flavones (Chemical & Pharmaceutical Bulletin (0009 - 2363, CPBTAL), 34,838 (1986)).

In addition, quercetin, which is a flavonol, has been reported to obstruct S.Mutans dextransucrase (Agricultural and Biological Chemistry (0002 - 1369, ABCHA6), 48 and 2143 (1984)).

In addition, flavonols, such as quercetin or myricetin, have been reported to inhibit the activity of glyoxalase I that participates in the inflammatory response have been reported (Noka magazine, 57,765 (1983)); in addition, there is a report of obstruction on xanthine oxidase, which is assumed to participate in gout, by flavones, such as apigenin and luteolin, and some glycosides and kaempferol and quercetin or other flavonols and glycosides of them (journal of natural medicine, 41,116 (1987)).

In addition, action on yeast α-glucosidase (Agricultural and Biological Chemistry (0002 - 1369, ABCHA6), 48 and 1559 (1984)) and alkaline phosphatase (Noka magazine, 54,171 (1980)) have been reported.

[0008]

As far as effects of flavonoids on lipase is concerned, there is only research on isoflavone from soybeans. In that case, it is only reported that soybean isoflavone obstructs lipase from soybean germination, but it displays weak obstruction on pancreatic lipase (Kumamoto Women's University abstracts, 33 and 60 (1981)).

[0009]

As per the above, there are a number of reports on flavonoids. However, there are no citations that state that the flavonoids that pertain to this invention display a lipase-inhibiting effect.

[0010]

[Problems to be Solved by the Invention]

The objective of the invention is to provide a very safe lipase-inhibiting agent that controls the digestion and absorption of lipids in-vivo and it will display very high inhibition against pancreatic lipase, which is a key factor in obesity; it will obstruct this [i.e., the lipase] and helps control and prevent obesity. In addition, it can be utilized in the prevention of deterioration of foodstuffs and unpleasant odors caused by lipase; and provide foods and beverages to which it is added.

[0011]

A search was made for many years for natural components that would be very safe and which would inhibit lipase. As a result, it was ascertained that that flavonoid that is shown in Formula (1) has a high lipase-inhibiting effect.

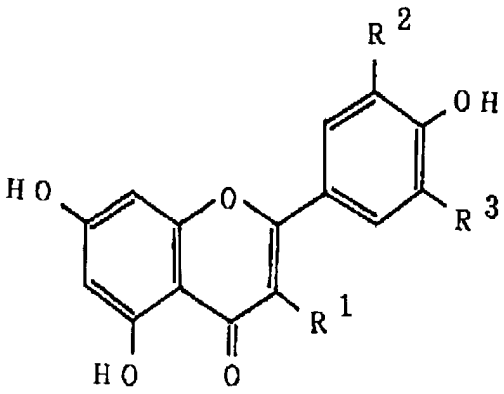
[0012]

[Means to Solve the Problems]

Based on this invention, there is the lipase inhibitor that is distinguished by the fact that it contains a flavonoid

[0013]

[Chemical Formula 2]



[I]

[0014]

that is shown in formula (1) (in the formula, R^1、 R^2 and R^3, are each independent and the show hydrogen atoms or hydroxyl groups) as the effective component of the lipase inhibitor.

[0015]

These flavonoids can be used alone or different kinds of them can be mixed together.

In addition, these flavonoids can be used as they are or they can be used as solutions diluted with appropriate solvents or as suspensions.

Moreover, with normal operations, such as mixing or drying, they can be used in powdered form or as pastes in mixtures with other additives.

[0016]

These flavonoids can be formulated appropriately and used as a lipase inhibitor.

In addition, they can be added or mixed beforehand into foods and used.

Moreover, these flavonoids can undergo appropriate distributed saccharification and be used.

[0017]

[Working Principle]

These flavonoids have a higher inhibiting effect than epigallocatechin gallate that is a component in green tea and which has been assumed to be high in lipase inhibition. At same time, since it is derived from natural plants, it provides a lipase inhibitor that is very safe.

[0018]

These lipase inhibitors can be utilized to prevent obesity as a result of the blockage of digestion and absorption of oils and fats, and, they can be used to prevent the deterioration of foods or the occurrence of unpleasant odors caused by lipase.

[0019]

[Working Example(s)]

This invention is explained in further detail below with the Working Examples. This invention, however, is not limited only to the Working Examples below.

[0020]

Working Example 1 (lipase activity measurement method)

Measurement of lipase activity is done by using an oleic acid ester of 4 -methyl umbelliferone (4 -MUO) that has fluorescent properties as the substrate and measuring the fluorescence of the 4 -methyl umbelliferone that has been produced by the reaction.

[0021]

100 μl of a 4-MUO suspension, the substrate, 50 μl of a pig pancreatic lipase (supplied by Sigma) solution, and 50 μl of a buffer solution are taken into a small test tube. Finally, 0.05 mM of 4-MUO、 2.2 μg of the pig pancreatic lipase, and a McIlvaine buffer solution (pH of 7.4) are allowed to react for twenty (20) minutes at 37 deg C.

1 ml of 0.1 N hydrochloric acid was added and the reaction was allowed to stop. 2 ml of 0.1 M sodium citrate was added so that the pH of the solution would be in the vicinity of 4.3. After that, the fluorescence in the 4-methyl umbelliferone (excitation wavelength of 320 nm; fluorescence wave length of 450 nm) that was produced by that reaction was measured by a fluorescence intensity meter.

[0022]

Working Example 2 (Measurement of the lipase-inhibiting effect)

The measurement of the inhibiting effects of the sample materials exerted on lipase activity was done by adding sample materials to the measuring system of the lipase activity, shown in the Working Example 1, and checking the effects on activity.

[0023]

Each sample was dissolved in 50% tetrahydrofuran (THF). 5 μl of the 50% THF solution of the sample materials was added instead of the 5 μl of the McIlvaine buffer in the reaction system that is shown in Working Example 1. The reaction was allowed to occur.

As far as the control group was concerned, 5 μl of the 50% THF solution was added and the reaction was allowed to occur in a similar manner.

Inhibitory activity was displayed by the amount of the sample materials added (IC_{50} (μg)) to reduce the activity of the control group, to which no sample had been added, to half.

[0024]

Working Example 3 (inhibiting effect of flavonoid)

In line with the above-mentioned Working Examples, the lipase-inhibiting effects of the flavonoids that pertain to the invention were studied.

Results are shown in Table 1.

[0025]

[Table 1]

フラボン類およびフラボノール類のリパーゼ阻害効果

試　料	構　造			IC_{50} (μg)
	R^1	R^2	R^3	
ルテオリン	H	OH	H	0.41
アピゲニン	H	H	H	0.25
ケンフェロール	OH	H	H	0.14
ケルセチン	OH	OH	H	0.60
ミリセチン	OH	OH	OH	0.51
エピガロカテキンガレート				1.0

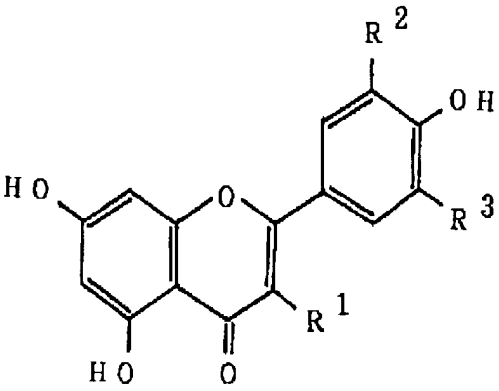
[Table 1: Translation]

Lipase-inhibiting effects of flavonoids and flavonols

Test materials	Structure			
Luteolin Apigenin Kaempferol Quercetin Myricetin				
Epigallocatechin gallate				

[0026]

[Chemical Formula 3]



[I]

[0027]

Epigallocatechin gallate, which is a main component of green tea, is known to be high in lipase-inhibiting effects. Inhibiting effects of the flavonoids that pertain to the invention were found to be clearly higher even than epigallocatechin gallate.

[0028]

[Effects of the Invention]

Based on this invention, a very safe lipase-inhibiting agent is provided that controls the digestion and absorption of lipids in-vivo and it displays a very high inhibition against pancreatic lipase, which is a key factor in obesity. It obstructs this [i.e., the lipase] and helps control and prevent obesity. In addition, it can be utilized in the prevention of deterioration of foodstuffs and the occurrence of unpleasant odors caused by lipase.

[0029]

With this invention, the lipase inhibitor in which flavonoid is an active ingredient has a higher lipase-inhibiting effect than epigallocatechin gallate, which is a component in green tea and is known to have lipase inhibitory activity, and it can obstruct the action of digestive enzyme lipase, control the digestion and absorption of lipids, and prevent obesity caused by the intake of fats.

.

[0030]

The lipase inhibitor in which flavonoid is as active ingredient that is based on the invention is not highly astringent like epigallocatechin gallate and it can be added or mixed without causing a deterioration in the flavor of foods.

In addition, very small amounts are contained in vegetables and beverage that are consumed daily. Therefore, it is a lipase inhibitor that is very safe.

Moreover, it can be utilized to prevent the deterioration of foodstuffs and the occurrence of unpleasant odors caused by lipase.